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CYP2D Microsatellite Polymorphism in Lewy Body Variant of Alzheimer's Disease and Parkinson's Disease

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The Lewy body variant (LBV) has been recognized as a distinct subset of Alzheimer's disease (AD). In this study, we conducted an allelic association study in patients with pure AD, LBV and also Parkinson's disease (PD) by using the CYP2D microsatellite, the (dG-dT)_n dinucleotide repeat (n = 16 - 27) located between CYP2D8P and CYP2D7 genes. The alleles longer than 21 repeat (the long-type alleles) were excessively represented in LBV (allele frequency, 0.313) compared with the age-matched control (0.186) (odds ratio = 1.99, p = 0.019 by χ^2 test). This overrepresentation was also found in PD (0.298) (odds ratio = 1.86, p = 0.037), but not in pure AD (0.196). The long-type alleles showed a strong association with the CYP2D6 B mutation (odds ratio = 88.50, p < 0.001 by Fisher's exact test), but not with the D mutation or the deletion of CYP2D6 gene. These findings confirmed a close association of the CYP2D locus with LBV and PD, indicating the following two possibilities: the involvement of the CYP2D6 B mutation in pathogenesis of LBV and PD in a dominant-negative manner; or the linkage disequilibrium of the CYP2D microsatellite to another pathogenic gene locus. The microsatellite of the CYP2D locus could be an informative marker in the genetic study of LBV as well as PD.

Keywords : CYP2D6 / Microsatellite / Alzheimer's disease / Parkinson's disease / Lewy body

Alzheimer's disease (AD) and Parkinson's disease (PD) are considered complex multifactorial diseases, with an interaction of genetic susceptibility [1, 2] and environmental factors against a background of aging. The Lewy body variant (LBV) represents a clinico-pathologically defined subset of AD. It is characterized by the presence of Lewy bodies (LBs) in neocortical and subcortical regions of the AD brain. The LB is an intracytoplasmic neuronal inclusion and a hallmark of idiopathic PD.

Genetic analyses have revealed the association of the CYP2D6 B mutation with PD. CYP2D6 codes for one form of cytochrome P450 enzyme, which is responsible for hydroxylation of several substances. The CYP2D gene cluster consists of CYP2D8P, CYP2D7 and CYP2D6 genes in the order from 5' to 3' on chromosome 22 at q13.1-13.2. The B mutation of the CYP2D6 gene is a G to A transition at the intron 3 - exon 4 junction, which shifts the position of the 3' splice site, leading to a frameshift.

BIOORGANIC CHEMISTRY — Molecular Clinical Chemistry —

Scope of research

This laboratory was founded in 1994 with the aim of linking (bio)chemical research and clinical medicine. Thus, the scope of our research encompasses the structure, function and regulation of various biomolecules, the pathophysiological significance of bioreactions in relation to human diseases, and the application of molecular techniques to clinical diagnosis and therapy. Our current interest is focused on poly(ADP-ribosyl)ation, nuclear (de)localization of proteins in association with apoptosis, and the molecular etiology of Alzheimer's disease and related disorders.



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and inactivation of this enzyme.

In the CYP2D gene locus, the microsatellite, a (dG-dT)_n dinucleotide repeat, is located between the CYP2D8P and CYP2D7 genes. In this allelic association study, we analyzed the CYP2D microsatellite in patients with pure AD, LBV and PD [3]. This microsatellite, which is in the linkage disequilibrium with the CYP2D6 B mutation, proved to be a useful marker for assessment of CYP2D6 gene involvement in LB-associated diseases (LBV and PD).

I. Polymorphism of the CYP2D microsatellite.

We found 12 alleles in the CYP2D microsatellite. The size of PCR products ranged from 96 to 118 bp (Figure 1). The number of (dG-dT)_n repeat ranged from 16 to 27. We named each allele A16 to A27 by the repeat number.

II. CYP2D microsatellite polymorphisms in pure AD, LBV and PD.

We then analyzed the distribution of allele frequencies of CYP2D microsatellites in the control and disease groups. The frequencies of the short- and long-type alleles were significantly asso-

ciated with the control and disease groups. The long-type allele was excessively represented in LBV (0.313) compared with control (0.186) or pure AD (0.196). The PD patients also showed this overrepresentation (0.298).

III. CYP2D microsatellite polymorphisms and CYP2D6 B mutation.

The allele frequencies of CYP2D microsatellites were associated with the CYP2D6 B mutation. Its frequency was significantly higher in LBV (0.281) than in control (0.157) or pure AD (0.175). The PD patients also showed a higher value (0.234), although the difference did not reach a significant level in this study.

IV. CYP2D microsatellite polymorphisms and CYP2D6 D mutation.

We analyzed XbaI RFLP in order to investigate a relationship between the structure of the CYP2D gene cluster and CYP2D microsatellite genotypes. Four haplotypes of XbaI RFLP were identified by Southern blot analysis. The 11.5-kb haplotype, or the D mutant allele (deletion mutation), was not associated with the long-type allele. The results of the XbaI RFLP study, combined with those of the PCR analysis, indicated no overrepresentation of the CYP2D6 D mutation in any disease groups.

These findings confirmed a close association of the CYP2D locus with LBV and PD, indicating the following two possibilities: the involvement of the CYP2D6 B mutation in pathogenesis of LBV and PD in a dominant-negative manner; or the linkage disequilibrium of the CYP2D microsatellite to another pathogenic gene locus. The microsatellite of the CYP2D locus could be an informative marker in the genetic study of LBV as well as PD.

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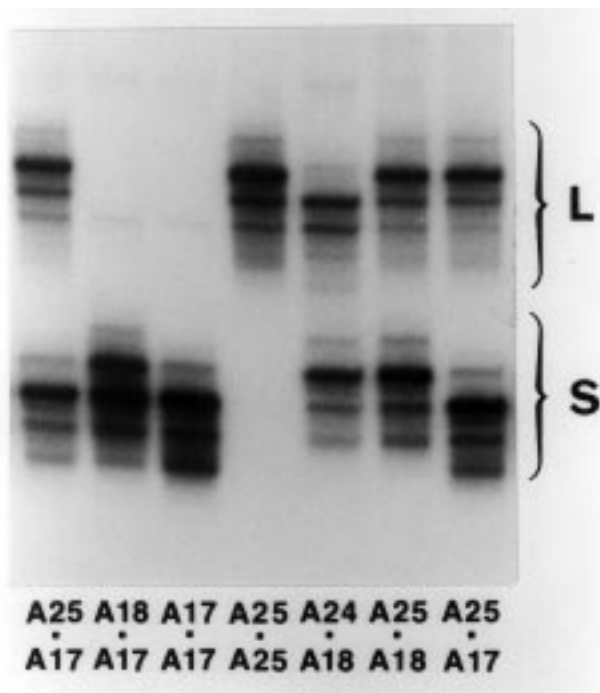


Figure 1. Autoradiogram of the CYP2D microsatellites. Genotypes are shown under respective lanes. The CYP2D microsatellite alleles were categorized into two groups; the short-type (A16 - A20) (S) and the long-type (A21 - A27) (L). The size of the A18 band was 100 bp. "Ghost" bands appeared, at 2-bp intervals, above and below the true band.